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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MCKENZIE, THOMAS C	
ART UNIT	PAPER NUMBER
1624	11

DATE MAILED: 09/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,009	BRAIN ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4 and 12-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-14,16 and 17* is/are allowed.

6)☒ Claim(s) *15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to amendments filed on 8/9/03. Applicant has canceled claims 2 and 5-11. Claims 12-17 are new. There are nine claims pending and eleven under consideration. Claims 1, 3, 4, 12, and 17 are compound claims. Claim 16 is a composition claim. Claim 15 is a use claim. Claims 13 and 14 are synthesis claims. This is the second action on the merits. The application concerns some carbonyl-piperidine and carbonyl-piperazine compounds, compositions, synthesis, and uses thereof.

Response to Amendment

2. Applicants new abstract overcomes the objection made in point #2 of the previous office action. Applicants' cancellation of claim 8 renders moot the objection made in point #3. Applicants cancellation of the affected claims renders moot the indefiniteness rejections made in points #4-#7. Applicants' deletion of prevention overcomes the enablement rejection made in point #8.

Claim Rejections - 35 USC § 112

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify

"a disease or condition in which is responsive to the antagonism of bradykinin activity".

It is unclear what diseases and treatments Applicants are intending to encompass. In the penultimate paragraph on page 21 Applicants list, using open language, some bradykinin B_1 associated diseases. What other diseases do they intend to treat? In the last paragraph on page 21, page 22, and the first three paragraphs on page 23, Applicants list a number of additional conditions they intend to treat. Are these also "a disease or condition in which is responsive to the antagonism of bradykinin activity"? Reference to the IgE receptor would suggest that asthma is not such a condition but what about psoriasis and eczema? There are two different bradykinin receptors, B_1 and B_2. The specification is silent concerning the B_2 associated diseases. Are these diseases also included?

US Patent 6,509,366 B2 states that vascular permeability, algesia, vasodilataion, hypotension associated with sepsis, and increased cell proliferation are such diseases. Applicants list none. It also says that the B_2 receptor is implicated in Type II diabetes. Are Applicants claiming treatment of that disease? US Patent 6,479,515 B1 states that septic and haemorrhagic shock, anaphylactic reactions, arthrosis, Crohn's disease, pancreatitis, certain carcinomas, hereditary angiooedema, migraine, encephalomyelitis, meningitis, cerebrovascular accidents

(especially those caused by a traumatic cerebral shock), certain neurological disorders, atherosclerosis, and can likewise be useful for potentiating antiviral agents. Again none of these conditions are mentioned in Applicants specification.

Determining whether a given disease responds or does not respond to such a receptor antagonist and thus, is covered by the claim language, can only be accomplished through potentially inconclusive clinical research. Suppose that a given drug, which has receptor antagonist properties *in vitro*, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or

lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus *iv* or in a time-release *po* formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active *in vitro*, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related receptor antagonists must be tried before one concludes that a specific disease does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of whom are receptor antagonists *in vitro*, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property that the second drug is capable. It is common for a drug, particularly in the CNS, to work by many mechanisms. The history of

psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to effect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some very different drug. There are for example, agents in antiviral and anticancer chemotherapy that are not themselves effective, but are effective treatments when the agents are combined with something else.

F. Even the most desired outcome does not unequivocally establish the meaning of the phrase. Our drug alone could be an effective treatment of the disease of interest. One still cannot conclude that the disease cured is a "bradykinin mediated disease". What if our drug has a second biological effect in addition to bradykinin receptor antagonism? It is possible that this second mechanism is responsible for the positive outcome.

Consequently, determining the true scope of the claim will require potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

The Examiner suggests using the specific diseases Applicants intend to treat using the passages cited above for support and being mindful of the enablement rejection made below.

Applicants argued concerning the rejection of claims 10 and 11 in point #8 of the previous office action that the new claim 15 narrowed the scope of the intended disease treatment to those diseases responding only to Applicants' antagonists. This is true but does not provide any art-recognized list of diseases to be treated as discussed above.

4. Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pain, does not reasonably provide enablement for treating bradykinin related diseases generally. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. The factors to be considered in making an enablement rejection were summarized in the previous office action.

a) Determining if any particular claimed compound would treat any particular bradykinin related disease disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials

with a number of fundamentally different diseases described in the previous point, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation. b) The direction concerning treating bradykinin related disease is found in the last two paragraphs on page 21, which merely states Applicants' intention to do so. Applicants describe formulations in the first and second paragraphs on page 24. These are prophetic and there is no working example of any formulation required to practice Applicants therapeutic claim. Doses required to practice their invention are described in the fourth paragraph on page 23. A 2,000-fold range of doses is recommended. Since no bradykinin antagonist has ever been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? There is an *in vitro* bradykinin B_1 binding assay described in pages 19 and 20 with no data. Applicants do not assert and it not art-recognized this assay is correlated to clinical efficacy for the treatment of all bradykinin related disease. There is an *in vivo* test on the tails of monkeys that is art-recognized as predictive of efficacy for the treatment of pain in humans described in the second and third paragraph on page 21. c) There is no working example of treatment of any disease in man or of any other disease in animals. d) The nature of the invention is clinical treatment of disease with bradykinin

antagonists, which involves physiological activity. e) Marceau (Pharmacol Rev.) summarizes the state of the clinical arts in bradykinin related diseases in the last complete sentence on page 19 that, "[p]ractically nothing is known about the clinical pharmacology of the B1R [the bradykinin B1 receptor]".

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the thousands of compounds of claim 1 as well as the unknown list of diseases embraced by the phrase responsive to bradykinin antagonists. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Allowable Subject Matter

5. Claims 1, 3, 4, 12-14, 16, and 17 are allowed.

Conclusion

6. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK